DETAILED ACTION

Claims 1-28 are pending in the application.

Applicant's election of Group III claims 1-15 and 20-23 in the reply filed on 1/28/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 16-19 and 24-28 are presently withdrawn from considerations as being non-elected subject matter. Claims 1-15 and 20-23 are under examination as they read upon the elected subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely

exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

In the present instance, claim 3 recites the broad recitation "about 25% methemoglobin", and the claim also recites lesser amounts of methemoblogin which are the narrower statements of the range/limitation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6-9, and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Henderson et al. (Abstract; Lancet 1972, 300(7788), pp 1162-1163) as evidenced by Hot dog nutrition facts.

Henderson et al. disclose in the abstract a patient eating frankfurters that contain nitrites as well as ingesting sodium nitrite solutions. The patient developed a headache from the oral ingestion of the frankfurters and nitrite. Since an effective amount of the same salt of nitrite as instantly claimed was used then it would inherently interact with hemoglobin to make nitric oxide and would produce methemoglobin and vasodilation

was induced and/or blood flow was increased in the subject as evidenced by the headache. Frankfurters comprise additional agents thus reading on instant claim 13. (See hot dog nutrition facts).

With respect to the limitations of instant claims 3, 4 and 6, The U.S. Patent Office is not equipped with analytical instruments to test prior art compositions for the infinite number of ways that a subsequent applicant may present previously unmeasured characteristics. When as here, the prior art appears to contain the exact same ingredients and applicant's own disclosure supports the suitability of the prior art composition as the inventive composition component, the burden is properly shifted to applicant to show otherwise.

Claim Rejections - 35 USC § 102

Claims 1-4, 6- 8, 11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Gale (US 4,849,226).

Gale disclose a method for increasing the supply of oxygen to the heart of a warm-blooded animal which comprises administering a vasodilator (Claim 1). Gale disclose sodium nitrite as a vasodilator thus anticipating instant claims 1, 7 and 8 (column 6 lines 54-55). In the absence of evidence to the contrary, the sodium nitrite is non-acidified. Gale disclose male volunteers thus reading on claims 11 and 12 (column 12, line 38). It is the Examiner's position that the sodium nitrite reacts in the presence of hemoglobin to release nitric oxide and anticipate instant claim 2.

With respect to the limitations of instant claims 3, 4 and 6, The U.S. Patent Office is not equipped with analytical instruments to test prior art compositions for the infinite number of ways that a subsequent applicant may present previously unmeasured characteristics. When as here, the prior art appears to contain the exact same ingredients and applicant's own disclosure supports the suitability of the prior art composition as the inventive composition component, the burden is properly shifted to applicant to show otherwise.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-15 and 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (Abstract: J. Cereb. Blood Flow Metab. 1994, 14(2), 217-

26) in view of Modin et al. (Acta Physiol Scand 2001, 171, 9-16 and,with respect to claims 13-15, Nachtsheim (West J Med. 1998, 169(2), 112-113).

Applicant claims a method for inducing vasodilation and/or increasing blood flow in a subject, comprising administering to the subject an effective amount of a non-acidified pharmaceutically-acceptable salt of nitrite for a sufficient period of time to induce vasodilation and/or increase blood flow in the subject.

Determination of the scope and content of the prior art

(MPEP 2141.01)

In the Abstract, Zhang et al. teach the use of **nitric oxide donors** to increase blood flow and reduce brain damage in focal **ischemia** (title). Zhang et al. teach the nitric oxide donors sodium nitroprusside (3 mg/kg/h) and 3-morpholino-sydnonimine (1.5-6 mg/kd/h) administered into the carotid artery of rats for 60 min. Zhang et al. teach and suggest that nitric oxide donors may represent a new therapeutic strategy for the management of acute stroke.

Modin et al. teach that nitric oxide is derived from nitrite (title). Modin et al. teach that the relaxatory effect of nitrite was increased at pH 6.6 over neutral pH (Abstract). Thus Modin et al. teach that **non-acidified nitrite** also has relaxatory effects similar to “acidified” nitrite (see figures 1, 2, figure 5 and respective discussion in the text). Modin et al. administered various amounts of **sodium nitrite** but noted a threshold response of

10 microM and near relaxation to basal tone at 1000 microM for the non-acidified sodium nitrite (page 11, Results). Modin et al. teach adding additional agents (ascorbic acid) to enhance the effect of the sodium nitrite (Abstract) Modin et al. conclude that inorganic nitrite evokes vasodilation most likely through nitric oxide release and that this effect is increased if the pH of the environment is reduced to levels normally found in tissues during **ischemia**/hypoxia (page 15, last paragraph).

Nachtsheim teaches that **sildenafil** is a known promoter of vasodilation that can enhance sexual experience (see whole article). Nachtsheim teaches that sildenafil works in conjunction with nitric oxide to enhance the vasodilatory effect. Nitric oxide signals cGMP production which then causes smooth muscle relaxation. Sildenafil blocks the enzyme responsible for degradation of cGMP thus leading to higher sustained levels of cGMP and relaxation of the smooth muscle (Page 112).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and Zhang et a. is that Zhang et al. do not expressly teach non-acidified sodium nitrite in the amount of 0.6 to 240 microM. These deficiency in Zhang et al. is cured by the teachings of Modin et al.

2. The difference between the instant application and Zhang et a. is that Zhang et al. do not expressly teach addition of sildenafil in the method. These deficiency in Nachtsheim.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use non-acidified sodium nitrite within the range instantly claimed, as suggested by Modin et al., in the method of Zhang et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because : 1) Zhang et al. suggest using other nitric oxide donors; and 2) Modin et al. suggest how much sodium nitrite, a known nitric oxide donor, would be beneficial for use in tissues during ischemia. Modin et al. teach carotid injection over 60 minutes of the sodium nitrite and other forms of administration such as parental, oral, bucal, rectal, ex vivo, or intraocular, peritoneal, intravenous, intraarterial, subcutaneous, inhaled, intramuscular or cardiopulmonary bypass circuit modes of adminstation are not only obvious to one of ordinary skill in the art of medicine but also merely result in the same thing; increasing the blood plasma levels of sodium nitrite, in the absence of evidence to the contrary. It is the Examiner's position that rats render obvious other mammals such as humans to one of ordinary skill in the art of medicine.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use sildenafil, as suggested by Nachtsheim, in the method of Zhang et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because it is established that sildenafil enhances the action of nitric oxide thus presenting an improved treatment protocol for the patient with the added benefit of potential enhanced sexual activity for the patient.

Summary: The ***concept*** of treating cerebral ischemia with nitric oxide donors to induce vasodilation and/or increase blood flow is established in the art. Non-acidified sodium nitrite is known to be a nitric oxide donor in the art. Applicant has merely followed the suggestions of Zhang et al. and Modin et al. to use sodium nitrite in the treatment of cerebral ischemia. The predictable expected result is induced vasodilation and increased blood flow in the subject.

From recent case law: "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." (KSR INTERNATIONAL CO. v. TELEFLEX INC. ET AL. 550 U. S. ____ (2007) page 24).

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed

invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6-13 and 20-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 11, and 13-15 of copending Application No. 10/563,683. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the instant invention embraces or is embraced by the subject matter of the

copending application. One of ordinary skill in the art would recognize the methods in the copending application of treating brain ischemia--reperfusion by decreasing blood pressure and or increasing vasodilation with a non-acidified sodium nitrite to a subject as embracing the subject matter of instant claims 1 and 20-23. The same concentrations of sodium nitrite are claimed as well as the subjects and routes of administration.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERNST V. ARNOLD whose telephone number is (571)272-8509. The examiner can normally be reached on M-F 6:15-3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ernst V Arnold/
Art Unit 1616